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10/540,193	06/20/2005	Dulce Elena Casarini	0002150USU/2417	2762

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EXAMINER	
CHEU, CHANGHWA J	
ART UNIT	**PAPER NUMBER**
1641	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/540,193	CASARINI ET AL.	
	Examiner	Art Unit	
	JACOB CHEU	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16 and 20-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16, 20-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Applicant's amendment filed on 1/28/2008 has been received and entered into record and considered.

The following information provided in the amendment affects the instant application:

1. Claims 17-19 have been cancelled.
2. Claims 23-26 have been added to the instant application.
3. Currently, claims 1-16, 20-26 are under examination.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 8-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

With Respect to claim 8, step (c), the recited Markush group is confusing.

Written Description

Organ Damage

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-16, 20-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The current invention directs to a method of detecting ACE (angiotension I converting enzyme) isoforms, e.g. 65, 90 and 190 kDa, in the samples of patients as indicators for diagnosis of hypertension and organ damage. However, in view of the experimental method and results, there is no support of using the above mentioned ACE isoform biomarkers as indicators of organ damage.

Based on the experiments, Applicant concluded in several places indicating that the 65, 90, 190 kDa, are ACE isoforms. Particularly, the 90 kDa only appear in the hypertensive patients, and could serve as an biomarker for hypertension diagnosis (See page 25, line 12-16; page 32, line 12-16; page 38, line 1-6). The only data refer to the organ are Table II, yet these data are not for organ damage, but for tissue distribution in adrenal, aorta, heart, lung, and kidney. No method or guidance of which organ or what criteria to measure organ damage is disclosed. No reasonable extrapolation with respect to the appearance of the ACE isoform to organ damage is discussed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, the court clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification needs "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. One cannot describe what one has not conceived. See *Fiddes v.*

Baird, 30 USPQ2d 1481 at 1483. In view of the specification, Applicant has not shown sufficient evidence that the ACE isoform can be as organ damage indicator.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

3. Claims 1-7, 13-16 and 23-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Casarini et al. (Intl. J. Biochem. Cell Biology 2001 Vol. 33, page 75-85) in view of .

Casarini et al. teach a method of identifying and quantifying of isoforms of angiotensin I converting enzymes (ACE) in biological fluids, e.g. urine (See Abstract). Casarini et al. teach collecting an aliquot of concentrated urine and submiting the samples to separation and Western blot analysis (See page 76 Method and Figure 5 for Western blot analysis). Casarini et al. identify different ACE isoforms, such as 65 kDa, 90 kDa and 190 kDa (See Abstract; page 79, right column first paragraph; Figure 5) where the 190 kDa and 65 kDa

are in normal individuals, and 90 kDa appears in hypertension people. Supra. Although Casarini et al. do not explicitly teach these are "*makers*" in characterizing the hypertension in individuals, one ordinary skill in the art in reviewing the teachings of Casarini, would have been motivated to use these 65, 90 and 190 kDa as the markers for screening hypertensive disease in patients with reasonable expectation of success because the reliability of sufficient sample size analysis conducted by Casarini et al. (80 patients), and the different profiling, i.e. 65, 90 and 190 kDa ACE isoforms, appears between normal and hypertension patients. Furthermore, with the readily available specific antibodies recognizing these 65, 90 and 190 ACE isoforms through the Western blot analysis, it merely requires routine practice in the field to screen the biological samples from the patients to identify the presence of the ACE isoforms.

With respect to claims 2, 24-26, 90 kDa is present in the biological fluid, i.e. urine, of the hypertensive patients, and thus can be a marker of a predisposed hypertension. Supra.

With respect to claim 3, Casarini et al. teach using Western blot where specific antibodies against somatic ACE isoform of 190 kDa and against N-domain of ACE isoform of 65 and 90 kDa are used for identification (See Figure 5).

With respect to claims 4, Casarini et al. teach collecting urine samples for analysis. Surpa.

With respect to claims 5-7, Casarini et al. also show that the two peaks eluted by chromatography, corresponding to 65 kDa and 190 kDa in normotensive individuals and no detection of 190 kDa, but only 65 kDa and 90 kDa appear in hypertensive patients (See Figure 5; page 83, right column, third paragraph and page 84, first paragraph; also the cited reference 19).

With respect to claims 13-15, it would have been obvious from the data done by Casarini et al. that the 90 kDa can a prognostic tool for hypertension marker for (See Results and Discussion; Abstract).

With respect to claim 16, Casarini et al. teach the target organ is the kidney (See Method).

4. Claims 20-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Casarini et al. in view of Zuk et al. (US 4208479).

With respect to "kit", Casarini et al. do not explicitly teach using a kit comprising the 65, 90 and 190 kDa marker for analysis of hypertension. Zuk et al. teach that in performing assays, it is convenient and to combine the necessary reagents together in a kit (column 22, lines 20-35). Zuk et al. further teach that this may improve assay accuracy.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have motivated Casarini et al. to place the 65, 90 and 190 kDa in a kit as taught by Zuk et al. for convenience and better accuracy for assaying the samples from hypertension patients.

5. Claims 8-9 and 11-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Casarini et al. in view of Hattori et al. (Hypertension 2000 Vol. 35, page 1284-1290 ; applicant submitted IDS informaiton).

It is noted that the instant independent claim 8 directs to use the same 65, 90 and 190 kDa as the biomarkers as claim 1 for detecting the hypertension in patients as discussed above by the Casarini et al. reference. The differences of claim 8 rest on the step (a) and (b) of where Applicant recites using a modified chromatographic technique for identification of these ACEs isoform.

Hattori et al. teach a method of identifying and quantifying of isoforms of angiotensin I converting enzymes (ACE) in tissues, cells and biological fluids, e.g. urine (See Abstract). Hattori et al. teach collecting an aliquot of concentrated urine with Tris-HCL 50 mM buffer, pH 8.0, submit to gel filtration in AcA-34 column equilibrated with Tris-HCL 50 mM buffer, concentrated NaCl 150 m, pH 8.0 (See Method, page 1285) and collect urine samples determining protein amount at A280 nm and measuring angiotensin I activity by using appropriate substrates, such as Hipuril-L-His-L-Leu and Z-Phe-His-Leu (See cited reference 22 by Friedland et al.). Hattori et al. also identify the same hypertensive genetic makers, 170 kDa, 90 kDa and 65 kDa (See Abstract). It is noted, although the samples were from infants by Hattori et al. study, the methodology of identifying of the same ACEs isoforms would still be applicable to one ordinary skill in the art for the intended usage.

Under the recent Supreme Court KSR case law, it is now apparent "obvious to try" may be an appropriate test in more situations. "When there is motivation to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it is likely the product not of innovation but of ordinary skill and common sense". In that instance the fact that a combination was obvious to try might show that it was obvious under 35 USC 103. See *KSR Int'l Co v. Teleflex Inc.*, 127 S. Ct. 1727; 82 USPQ 1385, 1397 (2007). The problem facing those in the art here was to isolate the ACEs isoforms, namely 65, 90 and 190 kDa, and there were a number of methodologies available to do so, at least both Casarini or Hattori et al. teach how to do so. The skilled artisan would have reason to try these methodologies with reasonable expectation that at least one would be successful. Thus, using different workable technique of Hattori et al. to identify ACE isoforms was "the product not of innovation but of ordinary skill and common sense."

With respect to claims 9, the profile of 190 and 65 kDa isoforms are detected in normotensive parents (See Carasini et al., page 84, first paragraph).

With respect to claim 10, three markers, 190, 90 and 65 kDa can be detected in normotensive individuals with hypertensive parents. Supra.

With respect to claim 11, the recitation indicates that the samples are from hypertensive individuals with hypertensive parents and the profiling of the ACEs include 90 and 65 kDa. It would be an inherent characteristic for method of Casarini et al. in view of Hattori et al. to detect the same 90 and 65 kDa in these individuals as long as these markers are present in the individuals.

Response to Applicant's Arguments

6. The rejections of claims 1, 2, 4-7, 13-22 under 35 U.S.C. 102(b) as being anticipated by Casarini et al. are withdrawn because Casarini et al. do not explicitly teach using the 65, 90 and 190 kDa as biomarkers for hypertension.

7. The rejections of claims 8-12 under 35 U.S.C. 103(a) as being unpatentable over Hattori et al. because Hattori et al. do not explicitly teach using the the 65, 90 and 190 kDa as biomarkers for hypertension.

8. Applicant's arguments with respect to claims 1-22 have been considered but are moot in view of the new ground(s) of rejection.

Casarini et al. reference

Applicant argues that Casarini et al. reference merely shown the difference of ACE isoforms in the normal and hypertensive patients. Applicant argues that Casarini et al. do not disclose a method of detecting a predisposed individual for developing hypertension. The reference merely hypothesizes that the 90 kDa ACE isoform may "play an important

role in the development of hypertension, and the presence of 170, 90 and 65 kDa, was not described in individuals predisposed to develop hypertension.

Applicant's arguments have been considered, but are not persuasive.

As set forth in this Office Action, Examiner already established prima facie obviousness rejection in view of Casarini et al. reference. With respect to the "hypothesis" arguments on the physiological role of the 90 kDa might play, it is merely on the "physiological role", e.g. mechanism associating with hypertension, this has nothing to do with use this 90 kDa as identification marker for hypertension. One ordinary skill in the art would not be deterred in applying this as the marker to identify hypertension. Based upon the sufficient patient number, i.e. 80, and the difference profiling of the ACE isoforms appear in both normal and hypertensive patients, one ordinary skill in the art would immediate contemplate using these ACEs isoform as markers to characterize hypertensive patients. Furthermore, with the well-known and widely practice art, such as specific antibodies recognizing these markers, it would have anticipated results when detecting the samples from hypertensive patients.

Hottori et al. reference

Applicant argues that ACE isoforms are purified and characterized from premature infants. Hottori et al. do not describe a method of detecting hypertensive disease by using the ACE isoforms.

Applicant's arguments have been considered, but are not persuasive.

It has been discussed in this Office Action that the combination of Casarini et al. with the teachings of Hottori et al. is mainly because both references teach detecting the ACE isoform from a biological samples from people. Examiner has acknowledged that the reference of Hottori et al. does not explicitly teach characterizing the ACE isoforms from

hypertensive patients. However, under KSR case law, it is now apparent "obvious to try" may be an appropriate test in more situations. "When there is motivation to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it is likely the product not of innovation but of ordinary skill and common sense". In that instance the fact that a combination was obvious to try might show that it was obvious under 35 USC 103. See *KSR Int'l Co v. Teleflex Inc.*, 127 S. Ct. 1727; 82 USPQ 1385, 1397 (2007). The problem facing those in the art here was to isolate the ACEs isoforms, namely 65, 90 and 190 kDa, and there were a number of methodologies available to do so, at least both Casarini or Hattori et al. references show to do so. The skilled artisan would have reason to try these methodologies with reasonable expectation that at least one would be successful. Thus, using different workable technique of Hattori et al. to identify ACE isoforms was "the product not of innovation but of ordinary skill and common sense."

1. The rejection of claim 3 under 35 USC 103 (a) as unpatentable over Casarini et al. in view of Karst et al. is withdrawn because Applicant has amended the claim and the step of using Western blot is taught by Casarini et al..

Conclusion

2. No claim is allowed.

3. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JACOB CHEU whose telephone number is (571)272-0814. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jacob Cheu/
Examiner, Art Unit 1641

/Long V Le/
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